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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/690,462	10/21/2003	James P. Snyder	007157/270549	4831

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EXAMINER	
BALASUBRAMANIAN, VENKATARAMAN	
ART UNIT	**PAPER NUMBER**
1624	

DATE MAILED: 11/03/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/690,462	SNYDER ET AL.	
	Examiner	Art Unit	
	Venkataraman Balasubramanian	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' response filed on 8/024/2005 is made of record. Claims 13-38 are pending. In view of applicant's response, the following apply.

Priority

The second application must be an application for a patent for an invention which is also disclosed in the first application (the parent or provisional application); the disclosure of the invention in the parent application and in the second application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ 2d 1077 (Fed. Cir. 1994).

In the instant case the provisional application dose not provide support for all subject matter embraced in the instant application. Hence, the priority to provisional application is not granted for examination of the instant application.

This passage is same as made in the previous office action. Applicants are reminded that they are not entitled for above said priority date.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 13-38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Following apply. Any claim not specifically rejected is rejected as being dependent on a rejected claim and share the same limitation.

1. Recitation of "carboxylic acid, carboxylic ester, carboxamide" in claims 1, 21, 26 and 34 in definition of X_1 and X_2 renders these claims indefinite as it is not clear what is intended. Note these are compounds as recited not groups. Further more the scope of carboxylic acid is not clear. As recited it can include any organic compound. An appropriate correction is needed.

This rejection is same as made in the previous office action. Applicant's argument to overcome this rejection is not persuasive. First of all, applicants have misinterpreted the rejection by arguing that the examiner had mischaracterized the definition of X_1 and X_2. It is in correct. The issue here is whether the "carboxylic acid, carboxylic ester, carboxamide" are groups or compounds. As recited they appear to be compounds. Hence, this rejection is proper and is maintained.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 26-38 are rejected under U.S.C. 112, first paragraph, because the specification while being enabling for treating breast cancer and human melanoma, does not reasonably provide enablement for treating any or all cancer. The specification does not enable any physician skilled in the art of medicine, to use the invention commensurate in scope with these claims for reasons of record. To repeat: The factors to be considered in making an enablement rejection have been summarized above.
The instant claims are drawn to "treating cancerous tissue" in general. The scope of the claims includes any or all cancer due to VEGF/TF inhibition activity including those yet

to be discovered as due said mode of action for which there is no enabling disclosure. In addition, the scope of these claims includes treatment of various cancers which is not adequately enabled solely based on the activity of the compounds provided in the specification at pages 42-52. The instant compounds are disclosed to have VEGF/TF inhibition activity and it is recited that the instant compounds are therefore useful in treating any or all cancer stated above for which applicants provide no competent evidence. However, the applicants have not provided any competent evidence that the instantly disclosed tests are highly predictive for all the uses disclosed and embraced by the claim language for the intended host. Moreover many if not most cancers , are very difficult to treat and despite the fact that there are many drugs including those cited in the specification, which can be used for same VEGF/TF inhibition activity.

The scope of the claims involves all of the thousands of compounds of claim 1 as well as the any or all cancer embraced by the terms cancerous tissue.

Proliferative disease would include benign tumors, malignant tumors, polyps, lumps, lesions, other pre-cancerous conditions, psoriasis, leukemia, the hyper proliferation of the gastric epithelium caused by the Helicobacter pylori infection of ulcers.

Cancer is just an umbrella term. Tumors vary from those so benign that they are never treated to those so virulent that all present therapy is useless.

No compound has ever been found to treat cancers of all types generally. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "compound" is contrary to

our present understanding of oncology. Cecil Textbook of Medicine states, "each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study" (see the enclosed article, page 1004). Different types of cancers affect different organs and have different methods of growth and harm to the body. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally. Note substantiation of utility and its scope is required when utility is "speculative", "sufficiently unusual" or not provided. See Ex parte Jovanovics, 211 USPQ 907, 909; In re Langer 183 USPQ 288. Also note Hoffman v. Klaus 9 USPQ 2d 1657 and Ex parte Powers 220 USPQ 925 regarding type of testing needed to support in vivo uses.

Next, applicant's attention is drawn to the Revised Interim Utility and Written Description Guidelines, at 64 FR 71427 and 71440 (December 21, 1999) wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed method treating solely based on the inhibitory activity disclosed for the compounds. The state of the art is indicative of the requirement for undue experimentation. See Chen et al. Thromb. Haemost. 86(1): 334-345, 2001.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence

or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention: Therapeutic use of the compounds in treating disorders/diseases that require VEGF/TF inhibition activity.

2) The state of the prior art: A very recent publication expressed that the VEGF/TF inhibition activity effects are unpredictable and are still exploratory. See Chen et al cited above.

3) The predictability or lack thereof in the art: Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use for r treating any or all condition of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

4) The amount of direction or guidance present and 5) the presence or absence of working examples: Specification has no working examples to show treating any or all cancerous tissue and the state of the art is that the effects of VEGF/TF inhibition activity are unpredictable.

6) The breadth of the claims: The instant claims embrace any or all proliferative diseases and cancers including those yet to be related to VEGF/TF inhibition activity .

7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the pharmaceutical use, for the reasons stated above.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of enzyme-inhibitor interactions in general, and the lack of working examples regarding the activity of the claimed compounds towards treating the variety of diseases of the instant claims, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was 'filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

This rejection is same as made in the previous office action except that claims 35-38 are also included in the present rejection. Applicants' argument to overcome this rejection is not persuasive.

First of all, instant method of use claims are Reach through Claims. Reach

through claims, in general have a format drawn to mechanistic, receptor binding or enzymatic functionality and thereby reach through any or all diseases, disorders or conditions for which they lack written description and enabling disclosure in the specification.

In the instant case, it appears that, because the instant compounds inhibit angiogenesis which are said to be present in cancer, it is implied that, based on cell inhibition of angiogenesis, any or all cancer can be treated with the instant compounds for which there is no adequate written description and enabling disclosure. In addition, the scope of the term cancer would include lung cancer, bone cancer, pancreatic cancer, skin cancer. cancer of the head or neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region. stomach cancer, colon cancer, breast cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system (CNS), primary CNS lymphoma, spinal axis tumors, brain stem glioma, pituitary adenoma, or a combination of one or more of the foregoing cancers, to name a few, which are not adequately enabled solely based on the activity of the compounds provided in the

specification. Besides the generic cancer, specification also recites a list of preferred cancers for which also there are enabling disclosure. The instant compounds are disclosed to have angiogenesis inhibitory activity and it is recited that the instant compounds are therefore useful in treating any or all cancer stated above for which applicants provide no competent evidence. It appears that the applicants are asserting that the embraced compounds because of their mode action as angiogenesis inhibitor that would be useful for all sorts of cancers. However, the applicants have not provided any competent evidence that the instantly disclosed tests are highly predictive for all the uses disclosed and embraced by the claim language for the intended host. Moreover many if not most of cancers, such as lung cancer, brain cancer, pancreatic cancer, colon cancer etc. are very difficult to treat and despite the fact that there are many anticancer drugs.

Note claims 36-38 are explicitly recited reach through claims, which implicitly embrace any or all diseases.

Secondly, the parent compound curcumin itself is known to have angiogenic property but have not emerged as agent for treating any or all cancer. There is no reason to expect that any curciminoid analogs would be useful for treating any or all cancer.

Thirdly, the fact that specification has support for human melanoma, human prostate cancer and human breast cancer, does not lend support to treating any or all cacner. As pointed in the above rejection there are variety of anticancer agents , which have only limited use in treating specific cancer and not all cancers.

Applicants' argument citing Adams and Ferstl et al., is therefore cannot be deemed as support for treating any or all cancers. In fact the focus of Adam et al. is evaluation of curcuminoids as angiogenesis inhibitors and the concluding paragraph clearly indicate of futuristic comments and not scope of enablement as asserted by the applicants.

Applicants have also interpreted Chen et al. to imply that any or all cancer can be treated with the instant curcuminoids. First of all, the Chen et al. relates to TF and VEGF and there is no teaching that any or all cancer can be treated with compounds exhibiting activity toward these. Secondly, the fact that Chen et al, have found TF and VEGF in non-small cell carcinoma by no means lend support that instant curcuminoid would be useful for treating any or all cancer. In fact the concluding paragraph of Chen et al., calls for further experimentation.

Finally, testing in NCI battery of assays is clearly meant to evaluate whether a compound shows activity toward which cell line and it is a screening assays. NCI database has large number of compounds with varying activity toward different cell lines. This by no means can be treated as scope of enablement for treating any or all cancer.

Hence, this rejection is proper is maintained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 26-28, 31, 34, 35 and 38 are rejected under 35 U.S.C. 102(b) as being anticipated by El-Subbagh et al. J. Med. Chem. 43: 2915-2921, 2000.

El-Subbagh et al. teaches several compounds, which include generically compounds, composition and the method of use claimed in the instant claims. See entire document especially see formula 13.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 13-15, 19-20 , 22-23, 25-28, 30, 32-33 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over El-Subbagh et al. J. Med. Chem. 43: 2915-2921, 2000.

El-Subbagh et al. teaches several compounds, which include generically compounds, composition and the method of use claimed in the instant claims. See entire document especially see formula 13.

While said compounds do not anticipate the scope of instant claims in view of the amendment to exclude alkyl form R_1 definition, they are very closely related having NH in the reference versus NCH_3 in the instant claims. However, compounds that differ only in having H vs Me on nitrogen are not deemed patentably distinct absent evidence of superior or unexpected properties. See Ex parte Weston 121 USPQ 428; In re Doebel 174 USPQ 156.

Thus, one skilled in the art at the time of the invention would have been motivated to make compounds that have methyl on the nitrogen and expect the these compounds to possess the utility in the instant case in view of the close structural similarity outlined above.

Applicants' argument to overcome this rejection when applied as 102 rejection by suggesting that the El-Subbagh et al ., is not prior art, is not persuasive. The subject matter embraced in the paper has been in public domain as it was presented in a meeting held at Saudi Arabia. See footnote on page 2015. Hence, El-Subbagh et al. is a proper prior art and the above rejection is proper.

As for applicants' argument that the reference shows only testing of compound 13 for HIV, it is clear from the reference that these compounds were designed for both antiviral and antitumoral activities as seen in third paragraph of page 2915. It should be noted that applicants have not tested all their compounds for anticancerous effect and

have implied testing some would be more than enough. The same reason also should be applied to the compounds taught by El-Subbagh.

Hence, this rejection is proper and is maintained.

Conclusion

Any inquiry concerning this communication from the examiner should be addressed to Venkataraman Balasubramanian (Bala) whose telephone number is (571) 272-0662. The examiner can normally be reached on Monday through Thursday from 8.00 AM to 6.00 PM. The Supervisory Patent Examiner (SPE) of the art unit 1624 is James O. Wilson, whose telephone number is 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned (703) 872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAG. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-2 17-9197 (toll-free).

Venkataraman Balasubramanian

10/30/2005